The Armed Forces Health Surveillance Center,
the U.S. Army Medical Research and Materiel Command
and OSD/Health Affairs

Optimizing Preventive Strategies and Malaria Diagnostics to Reduce the Impact of Malaria on US Military Forces

DOD Malaria Stakeholder Meeting

May 30-31, 2012
Bethesda, MD

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14. ABSTRACT
Despite the availability of effective prevention measures and a long organizational history of fighting the disease, malaria remains a threat to U.S. forces and their operations.1 These effective prevention practices and protective measures are not uniformly implemented to avert disease in the DoD. The Medical Surveillance Monthly Report documents the ever-increasing number of malaria cases acquired in Afghanistan 91 cases in 2011 the greatest number in the last nine years.2 Malaria consistently ranks as the most important infectious disease threat to the U.S. military3 and is a significant force health protection (FHP) issue before, during and after deployments. This stakeholder forum addressed topics of particular relevance to the DoD and force health protection, to include: primaquine chemo-prophylaxis, clinical decision support tools and knowledge management, and malaria rapid dia-gnostic tests (RDTs). The forum also included a comprehensive recap of the progress made since last years forum, including updates of the current DoD chemoprophylaxis policy, malaria clinical practice guidelines, and current efforts to ensure PPM compliance in troops.

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EXECUTIVE SUMMARY

Optimizing Preventive Strategies and Malaria Diagnostics to Reduce the Impact of Malaria on U.S. Military Forces

DoD Malaria Stakeholder Meeting

30-31 May 2012

Despite the availability of effective prevention measures and a long organizational history of fighting the disease, malaria remains a threat to U.S. forces and their operations.[1] These effective prevention practices and protective measures are not uniformly implemented to avert disease in the DoD. The Medical Surveillance Monthly Report documents the ever-increasing number of malaria cases acquired in Afghanistan— 91 cases in 2011 — the greatest number in the last nine years.[2] Malaria consistently ranks as the most important infectious disease threat to the U.S. military[3] and is a significant force health protection (FHP) issue before, during and after deployments.

In May 2012, the Armed Forces Health Surveillance Center (AFHSC) hosted its third in a series of DoD Malaria Stakeholder meetings at the Uniformed Services University in Bethesda, Maryland. Entitled **"Optimizing Preventive Strategies and Malaria Diagnostics to Reduce the Impact of Malaria on U.S. Military Forces"**, this forum was co-sponsored by the Office of the Secretary of Defense/Health Affairs (OSD/HA) and the U.S. Army Medical Research and Materiel Command (USAMRMC). Dr. George Taylor (Deputy, Assistant Secretary of Defense for Force Health Protection & Readiness) welcomed the participants from across the Armed Forces and charged them to find Tri-Service solutions to reduce the burden of malaria in our troops.

Participants represented a wide array of DoD organizations, including representatives from OSD/HA, geographical Combatant Commands, public health and headquarters commands of the U.S. Army, Air Force, Navy, and Marine Corps, along with members of the operational, public health, preventive medicine, infectious disease, entomology, pest management, education and training, laboratory, materiel and acquisitions, and research and development communities.

This year's DoD Malaria Stakeholder meeting was built upon the success and progress made from last year's 2011 DoD Malaria Stakeholder meeting. Significant discussion at that venue addressed: revising malaria chemoprophylaxis policy to potentially advocate for greater Malarone® use in high-risk areas; endorsing collaboration between the overseas laboratories and the training and education commands to improve malaria microscopy slide sets and training; identifying the need for more clinical decision support tools for deployed providers, specifically creating a malaria clinical practice guideline and diagnostic algorithm; and, pursuing better educational materials and products to improve compliance with personal protective measures (PPM). Issues highlighted as warranting further examination included having expeditionary diagnostic capability in theater, identifying a common location for the archival of DoD malaria resources, and examining the policy and practices surrounding primaquine use in U.S. forces returning from malaria endemic regions.

This 2-day 2012 Malaria Stakeholder meeting included didactic lectures and expert panels by DoD and academic subject matter experts, followed by frank open discussions. To address the many issues identified during last year's DoD Malaria Stakeholder meeting, this meeting's objectives were to:

- Provide an update regarding current malaria mitigation efforts in support of the Combatant Commands;
- Assess operational challenges in malaria diagnostics;
- Identify potential solutions to optimize malaria diagnostic modalities;
- Continue collaborations for the development of clinical decision support tools and inventory of DoD malaria resources;
- Clarify issues regarding primaquine terminal chemoprophylaxis.

Setting the stage for this forum was an account from Liberia demonstrating successful malaria

prevention interventions used in support of Operation Onward Liberty. Using a combination of known strategies and the incorporation of innovative means of accountability— leveraging a text message reporting system to ensure chemoprophylaxis compliance— malaria cases within the unit were eliminated. This vignette highlighted the success that is possible when leadership, accountability, and preventive medicine principles are effectively employed in a malaria-endemic deployed setting.

This stakeholder forum addressed topics of particular relevance to the DoD and force health protection, to include: primaquine chemoprophylaxis, clinical decision support tools and knowledge management, and malaria rapid diagnostic tests (RDTs). The forum also included a comprehensive recap of the progress made since last year's forum, including updates of the current DoD chemoprophylaxis policy, malaria clinical practice guidelines, and current efforts to ensure PPM compliance in troops. Areas of particular interest included:

1) **Primaquine policy**:
   Stakeholders agreed that presumptive antimalarial relapse therapy (PART) should continue to be a component of FHP but must be a risk-based decision. The CDC has determined that 30 mg primaquine for 14 days is more efficacious than the current FDA-approved 15 mg daily dose. This is problematic since the DoD is constrained by FDA dosing recommendations for FHP policy. Future efforts need to explore available options to provide allowance for the 30 mg dosing regimen, which will then dictate guidance, policy and clinical decision support tools.

2) **Clinical Decision Support Tools & Knowledge Management**:
   The need for a common location to archive DoD malaria resources was previously identified. The Deployment Health Clinical Center already hosts a malaria webpage that contains Tri-Service policies and directives, clinical guidance, fact sheets, education and training, and other related malaria links. The PDHealth website was deemed to be a suitable solution for centralizing malaria resources, and the stakeholders proposed a board of advisors to ensure website content was up-to-date. *See: www.pdhealth.mil/malaria.asp*

3) **Improving Current RDT Capability**:
   Participants identified the need for a field-deployable RDT, particularly in the absence of microscopy and/or trained malaria microscopists. Current FDA-cleared RDTs (Binax Now®) are categorized as high-complexity tests and may only be utilized in Role 3 and 4 military treatment facilities. An analysis of alternatives will be constructed and presented to MRMC leadership for consideration.

NEXT STEPS: Attendees were enthusiastic about the progress made at this meeting, with many projects in the development and implementation phases. The Armed Forces Pest Management Board is addressing PPM compliance through a media campaign and utilization of new technologies, particularly given the tech-savvy aptitude of our younger Service members. The Armed Forces Infectious Disease Society will publish their DoD Malaria/Febrile Patient Clinical Practice Guideline which serves as a clinical resource to deployed providers. As the deliberations continue regarding a revision to the chemoprophylaxis policy (drafted last year), issues regarding appropriate primaquine dosing will need to be addressed. The Deployment Health Clinical Center has been designated as the central DoD repository for malaria resources and will host a Tri-Service board of advisors to supervise content posted to their malaria webpage. Microscopy diagnostic training aids, developed by the DoD overseas laboratories, are being incorporated into the enlisted and laboratory officer training curricula. However, the way ahead in providing more expeditionary diagnostic capabilities to the deployed medical providers in theater needs further elucidation.

ACKNOWLEDGEMENTS: AFHSC would like to thank the symposium speakers and participants for their presentations and engaging discussions. Special appreciation is extended to Ms. Alaina Thomas for her invaluable administrative and technical support of this forum. The opinions expressed herein are the views of the authors and do not reflect the official position of the Department of Defense or any of its organizations.

[1] AFHSC. *Editorial: Malaria in the U.S. Armed Forces: A Persistent but Preventable Threat.* MSMR 2012; 19(1):12-13.

[2] AFHSC. *Update: Malaria, U.S. Armed Forces 2011.* MSMR 2012; 19(1):2-6.

[3] Burnette et al. *Infectious diseases investment decision evaluation algorithm: a quantitative algorithm for prioritization of naturally occurring infectious disease threats to the U.S. military.* Mil Med 2008; 173(2):174-81.

Proceedings of the 2012 DoD Malaria Stakeholder Meeting

1. Introduction and Updates

The workshop commenced with "**Introductory Remarks"** from CAPT Kevin Russell (Director, Armed Forces Health Surveillance Center (AFHSC)) who highlighted the importance of malaria to deployed troops and the importance of convening malaria stakeholders in a face-to-face fashion. Following CAPT Russell's opening remarks, Dr. George P. Taylor (Deputy Assistant Secretary for Force Health Protection and Readiness (FHP&R)) provided the **"Welcoming Address"** which focused on the tremendous impact of malaria on the Department of Defense, preventing malaria in deployed troops, and appropriately treating cases that occur.

Capt William Scott (Nellis AFB) set the stage for the 2012 DoD Malaria Stakeholder Meeting by discussing his experiences **"Optimizing Preventive Strategies on the Front Lines."** As chief medical officer assigned to Operation Onward Liberty, Capt Scott shared his successes and challenges in malaria prevention in Liberia. Upon his arrival, malaria prophylaxis accountability consisted of a paper checklist posted in the gym where Service members affirmed whether they had taken their daily prophylaxis. The 12 malaria cases in the previous calendar year reflected the haphazard emphasis on, and the lack of compliance with, malaria prevention. In light of this less-than-ideal system, Capt Scott initiated several operational changes, to include random bednet checks, permethrin-treated uniforms, mandatory DEET distribution, malaria quizzes at all-hands meetings, and distribution of malaria prevention handouts during troop in-processing.

Additionally, a text messaging system was introduced and was a notable success. Service members were required to report daily compliance with malaria chemoprophylaxis to the general medical officer (GMO) or senior medical officer on duty. This texting system was particularly helpful during mobilities, when Service members were geographically dispersed or remote. Capt Scott focused on leveraging troop buy-in and incentivized his units to garner compliance. However, he was quick to emphasize that technological solutions are not always the answer and that many of his interventions were low tech and merely provided leadership and accountability. As evidence of the effectiveness of his interventions, no cases of malaria occurred during Capt Scott's tenure.

CDR Annette Von Thun (AFHSC) provided a synopsis and **"Update from the 2011 DoD Malaria Stakeholder Meeting"**. She highlighted the main outcomes and accomplishments from last year's meeting, the interval progress that had been made, and some of the remaining items that intended to be addressed by this current meeting's curriculum. Results of the mini-surveys and evaluations were shared and provided a framework for the current meeting's discussions. A full review of these topics can be found in the *Proceedings of the 2011 DoD Malaria Stakeholder Meeting*.[1]

LTC Brigilda Teneza (AFHSC) presented an update on the **"Incidence of Malaria in the U.S. Armed Forces"** for the DoD in 2011. She described the standard case definition for malaria, as defined

[1] Available on AFHSC's website: (http://www.afhsc.mil/viewDocument?file=Training/2011_DOD_malaria_MeetingSynopsis.pdf)

by the AFHSC, and the limitations associated with administrative data. She noted that cases of malaria in the DoD had increased over the past three years, with *Plasmodium vivax* (*P. vivax*) comprising the majority of cases for which species-specific detail was documented. Most cases in 2011 were in the active component (87.1%), in the Army (79.8%) and male (97.6%), with the 20-24 year age group most at risk. The largest number of presumed malaria cases in 2011 came from Afghanistan (91 cases), followed by Africa (24 cases). Alternative and more inclusive case definitions have been considered by AFHSC and were recently published in the Military Surveillance Monthly Report (MSMR).[2] LTC Teneza concluded by highlighting that malaria is still an issue for the U.S. Armed Forces, which makes having the capability to prevent, recognize, and treat malaria of paramount importance.

COL Scott Stanek (ASD/HA) provided an update on the status to the **"DoD Chemoprophylaxis Policy"** that was drafted at last year's meeting which proposed: Malarone® as the drug of choice for high-transmission settings; Malarone® or doxycycline as equivalent drugs of choice for low-transmission settings; Malarone® as the preferred chemoprophylaxis agent for short-term deployments; and directly observed therapy in high-risk environments. The draft policy has been routed to the Services for comment and was briefed to the Force Health Protection Integration Council in July 2012. The current DoD policy has been criticized for being piecemeal and out of date. The most recent guidance (HA Policy 09-017) addresses concerns about mefloquine and identifies doxycycline as the drug of choice; however, healthcare providers frequently express frustration that access to Malarone® is often restricted by their pharmacy departments due to cost-concerns and the lack of policy supporting its use.[3] COL Stanek proposed a Quality Assurance Review to assess how the Services are implementing current chemoprophylaxis policy and screening for mefloquine suitability. Consistent and standardized chemoprophylaxis documentation is needed and there are concerns that the Services are not adequately screening or complying with the mefloquine policy requirements.

COL Colin Ohrt of the Walter Reed Army Institute of Research (WRAIR) presented an update on **"Generic Malarone® Availability."** Glenmark Pharmaceuticals recently won the right to market exclusivity for atovaquone-proguanil (ATP, generic Malarone®) for a duration of six months. Two other Indian companies are producing and marketing generic ATP, Cipla and Dazzle. Glenmark is a non-Trade Agreement Act company, and therefore the DoD cannot purchase from Glenmark; however, COL Ohrt pointed out that, despite the reduction in price that often accompanies a generically-branded medication, the DoD has a better financial agreement in place with GlaxoSmithKline for Malarone®.

The larger issue that arises with the production of ATP in generic form is the ability of the drug to become more ubiquitous in endemic areas due to its lowered cost. Medicines for Malaria Venture has stated that ATP could be available for as little as 25 cents a dose. Although the lowered cost is clearly advantageous for individuals seeking treatment, it could become a problem if not administered properly, particularly in malaria endemic countries. Substandard or fake ATP circulating in endemic

[2] The 2012 annual malaria issue of the MSMR is available at: http://www.afhsc.mil/viewMSMR?file=2012/v19_n01.pdf

[3] ASD(HA) Memorandum 09-017: Policy Memorandum on the Use of Mefloquine (Lariam®) as Malaria Prophylaxis (dated 4 Sep 09) is available at: http://www.health.mil/libraries/HA_Policies_and_Guidelines/09-017.pdf

countries, or ATP not taken as directed, could induce point mutations in the malaria parasite potentially resulting in parasite resistance and rendering ATP ineffective. It was noted that many of these countries rely heavily on tourism as a source of revenue, and therefore should be invested in maintaining the pharmacological success of ATP as an anti-malarial agent; however, neither the DoD nor, in many cases, the endemic countries themselves have any ability to affect the development of ATP resistance.

CAPT Steven Rankin of the Armed Forces Pest Management Board (AFPMB) provided an update on **"Personal Protective Measure (PPM) compliance and AFPMB Initiatives"**. CAPT Rankin's presentation focused on enhancing PPM compliance through the utilization of new technologies, particularly given the technological aptitude of our younger Services members. AFPMB is collaborating with the Telemedicine & Advanced Technology Research Center (TATRC) and Africa Command (USAFRICOM) to develop a new application for retraining troops deploying to malarious regions of USAFRICOM. Given the popularity of smart phones, web links and video clips, CAPT Rankin indicated that applications for Medical Stability Operations are being developed. Such applications could provide easily-accessible means for training young troops on the importance of PPM compliance. In addition to smart phone applications, AFPMB is meeting with the Defense Media Activity (DMA) to discuss the possibility of producing PPM infomercials to run on the Armed Forces Network (AFN) for Service members and dependents overseas.

Unable to attend in person, MAJ Jacob Johnson at U.S. Army Medical Research Unit Kenya (USAMRU-K) provided an update via telephone on the **"GEIS Malaria Surveillance Steering Committee's Diagnostics Training Initiative."** MAJ Johnson noted that this initiative is a multi-faceted program that encompasses three core areas: (1) training, (2) quality systems, and (3) reference materials. MAJ Johnson highlighted training accomplishments since 2004 noting that the Kisumu Malaria Diagnostics Center (MDC) has taught 62 microscopy courses, trained 1,134 laboratory technicians, trained and mentored over 20 facilitators, and has established three malaria microscopy training centers. As a result of preceding Malaria Stakeholder meetings, the MDC is coordinating with many of the other DoD research labs preparing standardized, validated malaria blood films (slides). These slides will be utilized by the DoD and host nation partners for training, testing, research, and quality control. The MDC is working with the Army Medical Department (AMEDD) to incorporate these malaria slide sets into their medical education curriculum. Additionally, MDC is piloting the production of dried blood tubes for quality control of rapid diagnostic tests (RDTs) in resource-limited and combat settings.

LTC Paul Mann (AMEDD) provided an **"Update on Malaria Microscopy in the AMEDD."** He noted that senior enlisted laboratory technicians received initial training in malaria microscopy during Medical Laboratory Technician (MLT) training. This training is considered "entry-level" and is insufficient to maintain competency in diagnostic malaria microscopy. The lack of malaria training was also noted to be an issue for incoming laboratory officers, particularly those trained in the civilian sector, since civilian universities do not teach the breadth and depth of tropical medicine that the military requires of its medics, laboratorians, and clinicians.

A multi-pronged approach is being initiated to address the current gap in malaria microscopy, including field trials of fluorescent microscopy (QBC ParaLens and F.A.S.T.); educating the direct

accession lab officers during Officer Basic Course; engaging the medical laboratory specialists in familiarization training during MLT phase II; and creating web-based and DVD/CD training and sustainment packages. To this end, a diagnostics slide set was sent from the MDC and is being digitized onto a DVD to enable deployed personnel access to malaria diagnostic aids.

Dr. Refaat Hanna (USAFRICOM) provided an update on the **"East-Africa Malaria Task Force (E-AMTF)."** Dr. Hanna gave an overview of the formation of the E-AMTF, noting that the Task Force objectives at inception included defining the necessary components for an effective malaria prevention program; defining standards against which each nation may identify critical needs; and defining additional programs for building health system capabilities and capacities. E-AMTF membership currently includes: Burundi, Kenya, Rwanda, Tanzania, Uganda, and South Sudan.

The inaugural E-AMTF meeting was held 7-8 December 2011 in Philadelphia, PA at the 60th Annual American Society for Tropical Medicine and Hygiene Conference. Each African country representative presented the challenges related to their military malaria programs during peacetime and deployments and identified malaria as the number one threat to their respective militaries. Among the accomplishments at this meeting were the crafting and ratification of the E-AMTF charter and by-laws.

The second E-AMTF meeting took place in Dar es Salaam, Tanzania in July 2012. The participants created a road map prioritizing and addressed the issues identified by a thorough gap analysis that was conducted by the E-AMTF members' critique of their military malaria programs. Various DoD subject matter experts provided guidance to the E-AMTF. Additionally, the products and discussions that occurred in these DoD Malaria Stakeholder meetings (e.g., chemoprophylaxis policy, malaria surveillance, PPM training, malaria diagnostic and treatment resources) dovetailed with, and will serve to advance, the E-AMTF objectives.

CAPT Jason Maguire, representing the Armed Forces Infectious Disease Society (AFIDS), provided an update on the **"New Malaria/Febrile Illness Clinical Practice Guidelines for the DoD."** The creation of DoD malaria treatment guidelines was a task undertaken by AFIDS at the request of the 2011 Malaria Stakeholders to address the need for greater clinical decision support tools for deployed providers. CAPT Maguire emphasized that this product is a clinical practice guideline (CPG), not a policy, and noted that the AFIDS recommendations are predicated upon the Infectious Diseases Society of America's (IDSA) criteria for quality of evidence. The CPG addresses: pre-deployment preparations; malaria epidemiology; clinical presentation and the assessment of severity; diagnostic testing in the military environment; anti-malarial regimens to include first/second-line, species-specific, empiric and prophylaxis failure treatment recommendations. CAPT Maguire provided a draft algorithm for evaluation and initial management of febrile illness in non-immune individuals with recent or current exposure in a malaria endemic region [Appendix A]. The intent is to finalize comments and then submit this malaria CPG for publication, with plans for wide dissemination to DoD personnel thereafter.

2. Clinical Decision Support Tools and Knowledge Management

During the 2011 DoD Malaria Stakeholder Meeting, substantial discussion was devoted to determining an appropriate venue to make pertinent malaria information available pre- and post-deployment. In this context, Dr. Mary Vaeth and Mr. Stacy Tucker (DoD Deployment Health Clinical Center (DHCC)) were invited to provide an **"Overview of www.PDHealth.mil, Web-Support for Deployment-Related Healthcare."** The PDHealth website is managed by the DHCC and serves as a comprehensive source of information for healthcare providers, Service members, veterans, and families. Topics address deployment health concerns and conditions (including malaria), health-related aspects of the deployment process, risk communication, deployment-related research, healthcare services, and patient and family support services. The deployment support section includes webpages on pre-deployment, re-deployment, deployment health assessments, deployment-related exposures, and specific deployments by operation and by country/region.

A malaria webpage already exists within the PDHealth website and contains Tri-Service policies and directives, clinical guidance, fact sheets, education and training, and other related links on malaria. In addition to the general malaria information, the PDHealth website also contains a separate webpage dedicated to information on mefloquine. Discussion ensued regarding the utilization of PDHealth as the central Tri-Service repository of malaria information for Service members. Stakeholders appreciated that adopting PDHealth as the Tri-Service archive does not preclude individuals Services from posting information on their own Service's websites.

Stakeholders were supportive of using the PDHealth.mil website to centralize resources, and a breakout session further defined the mechanism to support this process. The group recommended the formation of a board of advisors who would meet annually or semi-annually to assure that the content of the website was up-to-date and encompassed the appropriate information. At a minimum, this board should include representation from the Combatant Commands (CCMDs), Service public health hubs, the Coast Guard (if interested), and USUHS (Department of Preventive Medicine and Biometrics). The process by which the information would be funneled to DHCC was not delineated, but the annual board would come together and provide feedback to the DHCC website manager. USAPHC was designated the advisory board lead and will ensure periodic site content reviews are conducted. The group agreed that, whenever possible, malaria-related documents should be posted on open websites to avoid difficult-to-access CAC-enabled and AKO/DKO-restricted platforms.

3. Primaquine Chemoprophylaxis

Dr. Alan Magill of the Defense Advanced Research Projects Agency (DARPA) introduced the topic of **"Primaquine Chemoprophylaxis Dilemmas."** Primaquine is indicated for primary prophylaxis, radical cure, and as presumptive anti-relapse therapy (PART). PART is a treatment strategy unique to the U.S. military. Despite appearing the same under a microscope, *P. vivax* is a heterogeneous species and there are nuances between different strains that exhibit definite biologic differences in response to treatment, relapse pattern and frequency depending on where the infection was acquired. Two prototype *P. vivax* strains are Chesson (tropical) and Korean (temperate).

Current Centers for Disease Control and Prevention (CDC) recommendations for primaquine dosing are 30mg (base) for 14 days, but the U.S. Food and Drug Administration (FDA) has only approved 15mg (base) for 14 days. The questions remain: How much primaquine is enough primaquine, and does primaquine resistance really exist? Dr. Magill indicated that often drug failures are reported as resistance; however, given the biologic differences in the *P. vivax* parasite, sub-therapeutic dosing could be a larger factor than initially considered. Primaquine was approved in 1952, and the FDA has not changed its recommendations for primaquine dosing since the initial licensure of the drug, nor has it been in the pharmaceutical companies' self-interest to perform the necessary population-based studies to document this regimen's efficacy. Although it could be argued that the FDA merely regulates product manufacturing and the licensing of pharmaceuticals, (and therefore does not regulate the practice of medicine), the Presidential Executive Order 13139 [Appendix B] and DoD Instruction (DODI) 6200.02 [Appendix C] prohibit DoD from the off-label use of medications for force health protection (FHP) purposes.

Following Dr. Magill's primaquine primer, CAPT William Padgett (Headquarters Marine Corps) led a discussion of **"Primaquine Chemoprophylaxis – Way Ahead."** The group deliberated whether primaquine anti-relapse therapy should be part of a routine post-deployment regimen upon return from high-risk areas. This led to further discussion as to whether PART was an FHP issue, whether everyone leaving a malarious zone should be prescribed PART, or whether PART should be used with consideration given to the malaria species (*P. vivax* and *P. ovale*) present in any given malarious area.

In the subsequent breakout session, participants suggested that the DoD consider weight-based dosing and PART for engagements that require small numbers of troops. Stakeholders generated four cogent topics regarding PART. (1) Since the U.S. military is the only military that uses PART, substantial discussion centered on whether PART should be kept as a standard requirement. The group members felt strongly, particularly given the countries in which the U.S. Armed Forces serve, that PART needs to remain a key component of the U.S. military FHP plan. (2) Having determined that PART needed to remain a requirement in the U.S. military FHP plan, the group focused on the necessary parameters for integration into higher-level policy, noting that CDC guidance is not based on field military conditions, the number of bites experienced, or malaria cases known to have occurred in the unit. The group will explore clinical practice guidelines, algorithms, and lists of subject matter experts to support the decision making of a GMO when determining the execution of PART. (3) The dosing regimen for PART was further deliberated, noting that the current FDA approved dose was 15mg daily for two weeks, per the package insert, which conflicted with the CDC recommendation of 30mg daily for two weeks. Since FHP policy cannot officially endorse the off-label use of a medication, treatment with the higher dose of primaquine would only be permitted in the context of an individual patient-provider relationship. The group will further investigate the options available to allow for the consideration of 30mg dosing regimen. (4) No clear conclusions were reached on whether PART needs to be a stand-alone DoD policy, integrated into existing DoD malaria policy, pushed to the Services, or left to the CCMD Surgeon's discretion. Determining how to incorporate PART into DoD policy is largely dependent on the dosing regimen (30mg vs. 15mg) and how that regimen is approved (DoD-level vs. Service-level vs. CCMD-level).

Ultimately, the PART dosage change should be the main effort going forward, and will be the basis for all other PART policy changes.

4. Diagnostic Challenges

Maj Robert Holmes (USAFRICOM) presented on **"Perceived Problems with Malaria Diagnostic Options in the Operational Environment."** Maj Holmes underscored the difficulty in finding local practitioners with malaria expertise in African countries, and that to use a local microscopist who also doubles as the apothecary is a dubious practice. The DoD has the need for highly sensitive rapid diagnostic tests that can be used in an operational setting by non-clinicians. Currently the only FDA-cleared RDT (BinaxNOW®) lacks sensitivity (especially for *P. vivax*), is not heat-stable, and its packaging does not meet field requirements (25-kit minimum). Additionally, it lacks an inherent positive control, is a moderate complexity test that requires a trained laboratorian in a Role 3 medical care facility, and the FDA requires microscopy for confirmatory testing of all specimens that test negative.

Maj Holmes' presentation segued into a larger panel discussion which addressed **"Diagnostic Challenges: Perspectives from the Front Lines"** and the malaria diagnostic issues that continue to be particularly problematic in the field**.** The panelists included CAPT Mark Malakooti (NAVAF), LTC Christine Lang (USASOC), LTC Laura Pacha (USAPHC), LCDR Jean-Paul Chretien (II MEF), Capt William Scott (Nellis AFB), and HMCM Mitchell Pearce (NECC). Participants debated the merits of the BinaxNOW® RDT and the practice of empirically treating patients if presenting with a febrile illness while deployed to a malarious region. The sensitivity of the test to heat degradation was a topic of discussion, as was the issue that BinaxNOW® RDTs only have one bottle of reagent per box of 25 kits, making the kit rather unwieldy for field operations.

Discussion arose regarding the distinction between Role 1 and Role 2 asset regulations. The FDA's regulations only apply to tests conducted inside the United States. Participants underscored the need for clarification on Level I vs. Level II products that could be purchased CONUS using Operations & Maintenance (O&M) funds and then placed overseas. The development of a simple algorithm to address febrile illness in malarious regions was proposed to provide young GMOs and medics a solution to the RDT sensitivity issue, noting that the consequences of erroneous treatment for presumed malaria are far less than the consequences of not treating for malaria, and that no matter how high the levels of parasitemia in the blood, a negative RDT result can never be completely trusted.

Addressing the theme of **"Current** research and development (R&D) **Efforts Addressing Malaria Diagnostics,"** LTC Phil Smith of U.S. Army Medical Research & Materiel Command (USAMRMC) provided background on **"MRMC's Decision Gate and the Materiel Development and Acquisition Process"**. He discussed medical product acquisition, how money is invested, how USAMRMC oversees the investment of product development money, and the assessment of whether developed products are meeting end-user needs. USAMRMC implements "Decision Gate," a management support framework that defines the medical product development lifecycle. Decision Gate helps identify, verify, and validate true materiel gaps; establishes a review process to ensure cost and schedule progress; helps ensure investments are made with a portfolio perspective; and facilitates engagement of all stakeholders.

In addition to Decision Gate, USAMRMC has created defined Biomedical Technology Readiness Levels (TRLs). TRLs provide a systematic way to assess and communicate to the Milestone Decision Authority (MDA) the maturity level of a particular technology and the maturity necessary for successful product advancement. BinaxNOW® falls within TRL 9, "Post-marketing studies/surveillance."

MAJ Tom Palys (WRAIR, Chair of the Military Infectious Diseases Research Program (MIDRP) Integrated Process Team (IPT)) briefed on the **"MIDRP Malaria Diagnostics Efforts."** The mission of the MIDRP diagnostics program is to develop FDA-cleared RDTs or hospital-based diagnostic assays for naturally occurring infectious diseases of military importance. The program is executed by WRAIR, Naval Medical Research Center (NMRC), and the overseas laboratories (AFRIMS, USAMRU-K, NAMRU-6, NAMRU-3, and NAMRU-2). The Tri-Service Infectious Disease Threats to the U.S. Military Prioritization Panel has ranked 38 infectious disease threats, placing higher priority on those diseases that have no vaccine or prophylactic treatment, for which there is no available field-deployable diagnostic capability, and which have the greatest potential to hinder troop strength.

Over the last ten years, seven percent ($1.618 million) of MIDRP diagnostic funding has been directed to malaria diagnostics. From 2006 - 2009, the MIDRP diagnostics program—in collaboration with AFRIMS—funded the species-specific malaria PCR assay for the Joint Biological Agent Identification and Detection System (JBAIDS). In 2007, with NMRC, the MIDRP diagnostics program provided support for a Multiplex RDT to identify fever causing pathogens in the blood, but the performance of this assay was deemed inadequate and funding was discontinued. Additionally, MIDRP funded a malaria species-specific loop-mediated isothermal amplification and oligoimmunochromatographic combination RDT. Although $155,000 was allocated for malaria diagnostics in 2012, no funds were designated for malaria diagnostics in 2013. So although malaria is currently the top infectious disease threat, USAMRMC has been focusing their efforts on other diseases since there is an existing FDA-cleared RDT product and medications available for both prevention and treatment.

Mr. Lou Jasper (U.S. Army Medical & Material Development Activity (USAMMDA)) briefed on the **"History of RDT Approval in the U.S. Military."** In June 2007, BinaxNOW® malaria RDT was cleared for use by the FDA.[4] Following its clearance, in September 2009 the FDA cleared the external positive control and re-categorized the BinaxNOW® malaria RDT from a high complexity test to a moderate complexity test under the Clinical Laboratory Improvement Amendments (CLIA). Mr. Jasper highlighted the challenges of obtaining an RDT that could be considered a low complexity test – either via achievement of CLIA-waived status or via the development of a truly low-complexity RDT that can be fielded as a Role 1 medical asset [Appendix D].

Continuing the theme of current R&D efforts in malaria diagnostics, COL Ohrt briefed meeting participants on **"New Technologies for the Tracking of Malaria in Deployed Troops."** COL Ohrt highlighted the novel technologies developed by Amethyst Technologies, Fio Corporation, and Johns Hopkins University Applied Physics Lab (JHU/APL). The Fio Corporation has developed a Smartreader

[4] BinaxNOW Malaria test overview, documentation, and support information is available at: http://www.alere.com/us/en/product-details/binaxnow-malaria.html

that enables real-time quality improvement and tracking of malaria in deployed troops. The Smartreader is a device that can be programmed and calibrated to read RDTs and provide an automated diagnosis. Clinical data is then captured on the touch screen interface and can be electronically stored and/or mailed to a secondary reviewer. The JHU/APL Suite for Automated Global Electronic Biosurveillance (SAGES) initiative is a platform that allows for syndromic data to be collected and transmitted via smart phones. SAGES works particularly well in resource-limited areas. These technologies could be utilized to improve malaria surveillance and diagnosis in deployed troops or troops serving in areas with limited diagnostics and has already been implemented in Kenya and Cameroon for other comprehensive disease surveillance purposes.

Dr. Martina Siwek (Chemical Biological Medical Systems (CBMS)) presented a briefing on the **"Next Generation Diagnostics System (NGDS)."** CBMS is seeking replacement technology for JBAIDS which is to be phased out by 2017 with the expectation that malaria will be incorporated into its NGDS platform. The NGDS development strategy for the replacement of JBAIDS is an interagency effort that involves the development of both a deployable and a Service laboratory component.

The deployable component would ideally be a commercial, off-the-shelf (COTS), FDA-cleared diagnostic system with improved analytical capacity and operational suitability. The deployable component would have maximum potential for rapid and affordable future capability growth to support diagnostics, surveillance and environmental detection of biological threats. The Service lab component would leverage existing laboratory infrastructure and be capable of identifying emerging, enhanced, and advanced threats. The aim of the Service lab component is to reduce the time to novel pathogen discovery by supporting rapid diagnostics development on other NGDS components. Ideally, the Service lab component would provide robust, in-country analytical capability. Such a component would be capable of being forward deployed, have reach-back potential, and be able to be utilized in a contingency-response capacity. The next evolution would have advanced capabilities that include low-complexity diagnostics and surveillance (capable of being used in a Role 1 or 2 medical support capacity); be capable of chemical, radiological and toxin exposure diagnoses; contain pre-symptomatic diagnostics; and have novel pathogen discovery capabilities.

To provide additional information on future malaria diagnostic efforts, Dr. Brad Ringeisen (Defense Threat Reduction Agency (DTRA)) gave a presentation on the **"DTRA 24-Month Diagnostic Device Challenge."** The objective of the 24-month challenge is an interim demonstration at the OCONUS labs, of an informatics-based, bio-surveillance ecosystem linked to ubiquitous, self-administered diagnostics capability. A "decision engine" is envisioned to use artificial intelligence to interpret data from the diagnostic system and return results with appropriate guidance to the individual. The decision engine will be leveraged to remove individual interpretation from the process to ensure accuracy, and will serve as the link between the diagnostics systems and the information management ecosystem.

Point-of-need diagnostic systems are proposed and will be developed for self-use or buddy care (Role 0) for use by non-medically trained Service members, with complexity akin to the home pregnancy test. Additionally, a Role 1 device for medics, corpsmen, and technicians will be engineered to provide

forward medical care in the deployed environment. The 24-month challenge OCONUS field demonstrations are expected to perform in a real-world setting of endemic and/or epidemic diseases, and is planned to have FDA clearance and CLIA-waived status. The preliminary malaria clinical test sites for the 24-month challenge will include NAMRU-2 (Cambodia), USAMRU-K (Kenya), NAMRU-3 (Egypt) and Nigeria (WRAIR collaborative site).

Dr. Valerie D'Acremont of the Swiss Tropical and Public Health Institute telephonically provided a guest lecture on the **"Robustness of Existing Malaria RDTs: Is Confirmatory Testing Necessary?"** Dr. D'Acremont presented data from studies in Africa, Europe, and the United States regarding the sensitivity of RDTs versus the "gold standard" blood film microscopy for malaria diagnosis.[5] She noted that positivity rates can be partially explained by patients' parasitemia, which is dependent on many variables, including pre-existing host immunity against malaria. Comparing RDTs with microscopy as the gold-standard is generally not appropriate because RDTs measure antigen levels, whereas microscopy measures parasite densities; therefore, exact congruence is not possible for the RDT. Additionally, many false positives attributed to RDTs are actually true positives, and merely reflect the tremendous sensitivity of the RDT. BinaxNOW® compared with other RDTs fared well in assessments of *Plasmodium falciparum* (*P. falciparum*) sensitivity, but was considered subpar when analyzed for its *P. vivax* sensitivity [Appendix E].[6]

The safety of making clinical management decisions solely on RDT test results was also addressed by Dr. D'Acremont. She presented data from numerous studies which demonstrated that no adverse outcomes were associated with false negative RDT results in nearly 10,000 children.[7,8,9] In returning travelers suspected of malaria, RDT-based algorithms in the setting of delayed (i.e., next day) microscopy demonstrated that clinical decisions could safely be made based solely on RDT results.

One reason motivating the use of RDTs for confirmatory testing for malaria is the need to reduce the amount of anti-malarial medication being erroneously prescribed, to reduce the selective pressures driving anti-malarial drug resistance. The impact of RDT implementation on malaria drug consumption in endemic countries has been profound. Implementation of an RDT in Tanzania was piloted in three district hospitals, three healthcare centers, and three dispensaries from 2006 to 2008. Prescriptions for anti-malarial medications significantly decreased from 81% to 24%. Unfortunately, antibiotic prescriptions increased modestly from 49% to 73%, indicating that, although RDTs provided

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[5] Ochola LB, Vounatsou P, Smith T, et al. The reliability of diagnostic techniques in the diagnosis and management of malaria in the absence of a gold standard. *Lancet Infect Dis.* 2006; 6(9): 582-588.

[6] A Foundation for Innovative New Diagnostics (FIND) interactive comparison of malaria RDT sensitivities and specificities is available at: http://www.finddiagnostics.org/programs/malaria-afs/malaria/rdt_quality_control/product_testing/interactive-guide/index.jsp

[7] Yeboah-Antwi K, Pilingana P, Macleod WB, et al. Community case management of fever due to malaria and pneumonia in children under five in Zambia: a cluster randomized controlled trial. *PLoS Med.* 2010; 7(9): e1000340.

[8] Msellem MI, Martensson A, Rotllant G, et al. Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanizibar – a crossover validation study. *PLoS Med.* 2009; 6(4): e1000070.

[9] D'Acremont V, Malila A, Swai N, et al. Withholding antimalarials in febrile children who have a negative result for a rapid diagnostic test. *Clin Infect Dis.* 2010; 51(5): 506-511.

healthcare workers with a more solid understanding of which patients did not have malaria, providers were still inclined to dispense medications without any evidence of microbial infection.[10]

Prior to the DoD Stakeholder Meeting, a multi-disciplinary group of experts convened to explore and scrutinize available options to address the perceived RDT shortcomings. CDR Von Thun elaborated upon the **"Possible Diagnostic Solutions for the RDT Capability,"** noting that there are two major types of approaches: packaging solutions and performance solutions. Packaging solutions could include changing manufacturer packaging such that fewer tests are included in each box, thereby reducing the footprint of the package (5-pack box already manufactured and available OCONUS); changing kit contents to make more operational friendly (to include lancets, multiple reagent bottles, etc.); and incorporating an external positive control to meet operational needs (CDC has dried cultured blood product that is temperature stable). Additionally, it was proposed that the package insert could be clarified to reflect DoD field use (i.e., microscopy at next available opportunity or echelon of care). A precedent has already been set with the Japanese Encephalitis vaccine which has both civilian and DoD package inserts for the identically-manufactured product. These potential solutions would be considered relatively short-term alternatives in lieu of a more permanent, performance solution.

Performance solutions would address issues of the test's inferior sensitivity and could potentially include: reformatting and modernization of the existing BinaxNOW® RDT; selection, and bringing to market, of another COTS product; or development of a second-generation RDT. Modernization of an existing capability can address many of the post-marketing issues associated with BinaxNOW® and wouldn't require the creation of new requirement documents as would the other two alternatives—although all options would require additional clinical trials to document efficacy. Whereas developing a second-generation RDT would be a long-term process, revising the current RDT or bringing a new, first-generation RDT to market would provide a more intermediate solution.

Options and constraints pertaining to the Clinical Laboratory Improvement Program (CLIP) manual and CLIA waivers were clarified. The CLIP manual can be modified only as may be required to meet the unique aspects of DoD missions, according to DODI 6440.2 [Appendix F]; however, CAPT Wilkerson (TMA/OCMO) explained that there is no such thing as a waiver of CLIA requirements. A "CLIA waiver" is a package that a vendor submits to the FDA in order to request that a moderate complexity device be placed in a "waived category" regarding restrictions of use for that device or test. In DoD's agreement with the U.S. Department of Health and Human Services (DHHS), CLIA regulations are implemented via CLIP, and a lab is defined as a person, place, or locale that is conducting medical diagnostic work to provide a result to a clinician to make a clinical diagnostic decisions.

Another participant noted that only force health protection (FHP) issues were required to abide by FDA regulations. Any universal FHP measures, such as required medications or required vaccinations, must abide by FDA on-label instructions; however, the practice of medicine in an individual patient-provider relationship is not beholden to FDA regulations because individual patient care would no longer be considered part of a FHP directive.

[10] D'Acremont V, Kahama-Maro J, Swai N, et al. Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. *Malaria J.* 2011; 10:107.

Mr. Lou Jasper from USAMMDA led the culminating discussion on **"Defining the Requirements for RDTs."** The goal of the discussion was to determine how best to address the gaps identified throughout the 2012 Stakeholder Meeting and to ensure that the proposed solutions meet the field requirements and receive the necessary attention from DoD policy makers. The ultimate objective is to be able to provide a field-expedient rapid diagnostic capability that offers suitable sensitivity, robustness (with positive controls), and environmental stability. The rapid diagnostic capability must also be able to be utilized at the level of the medic, corpsman, and technician. With this objective in mind, participants of the 2012 Stakeholder Meeting recommended:

(a) All affected CCMD Surgeons will draft a letter to be vetted to USAMRMC stating the importance of approving a rapid diagnostic product that can be used for malaria diagnosis in the field by individuals with minimal medical expertise;

(b) A working group should be established to determine whether a materiel or non-materiel solution is required to field an RDT. This working group should consist of a technician-based human diagnostics IPT with the addition of subject matter experts to contribute to a survey that will help refine the need for an RDT.

5. Conclusions and Way Forward

There are many facets to the DoD malaria prevention program, with each of the various communities playing essential but unique roles. This 2012 DoD Malaria Stakeholder Meeting brought together numerous Service, specialty, COCOM and operational experts including representatives from the public health, preventive medicine, infectious disease, entomology, pest management, education and training, laboratory, materiel and acquisitions, and research and development communities. These Stakeholders convened to strategize how best to improve and optimize the DoD's malaria program.

Many of the initiatives addressed in this forum are currently in the development and implementation phases. The Armed Forces Pest Management Board is addressing PPM compliance through a media campaign and utilization of new technologies, particularly given the tech-savvy aptitude of our younger Service members. The Armed Forces Infectious Disease Society will publish their DoD Malaria/Febrile Patient Clinical Practice Guideline which serves as a clinical resource to deployed providers. The Defense Health Clinical Center's PDHealth website has been designated as the central DoD repository for malaria resources and will host a Tri-Service board of advisors to supervise content posted to their malaria webpage. Microscopy diagnostic training aids, developed by the DoD overseas laboratories, are being incorporated into the enlisted and laboratory officer training curricula. As the deliberations continue regarding a revision to the chemoprophylaxis policy (drafted in 2011), issues regarding appropriate primaquine dosing will need to be addressed.

However, the way ahead in providing more expeditionary diagnostic capabilities to the deployed medical providers in theater still needs to be elucidated. The desired output from this meeting is securing support for a rapid diagnostic product that the medics and corpsmen can use for diagnoses of malaria in a forward deployed capacity without the need for microscopy confirmation.

This series of Malaria Stakeholder Meetings has provided the opportunity to address many operationally relevant issues and has benefited from having critical stakeholders in attendance. Attendees were enthusiastic about the progress made at these meetings; strategies have been outlined for each of the topics, and stakeholders are continuing to work independently to capitalize upon the momentum generated. Certainly there are growth opportunities still to be realized, but it is hoped that these conversations and ongoing efforts have had impact and will result in significant progress in further meeting the needs of our warfighters and deployed medical personnel with the objective of diminishing the impact of malaria on U.S. Forces.

Appendix A: Diagnosis and Management of Malaria in U.S. Military Personnel in Resource Limited Setting: Clinical Practice Guidelines by the Armed Forces Infectious Disease Society

Diagnosis and Management of Malaria in U.S. Military Personnel in Resource Limited Settings: Clinical Practice Guidelines by the Armed Forces Infectious Disease Society

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PREAMBLE

Evidence-based guidelines for the diagnosis and management of malaria in military service members were prepared by an expert panel of the Armed Forces Infectious Disease Society (AFIDS). The guidelines are intended for use by clinicians and other health care practitioners (including medics and corpsmen) caring for non-pregnant, adult United States (U.S.) military members in resource-limited settings who have febrile illness while in, or shortly after returning from, a malaria endemic location. They are not intended to guide care of foreign nationals who may be semi-immune, children, pregnant women, or those receiving care in a tertiary care medical setting. Information is provided about pre-deployment training and preparation, epidemiology, clinical manifestations, diagnosis, treatment, counterfeit and substandard medications, treatment setting and available resources. Tables list the doses and durations of anti-malarial therapies recommended by the Centers for Disease Control and Prevention (CDC) as well as those recommended by the World Health Organization (WHO). Deviation from CDC and WHO recommendations regarding what is considered first or second line therapy, is based on the evidence as well as consideration of the unique military population intended to benefit from these guidelines.

EXECUTIVE SUMMARY

Military service members deployed to malaria endemic areas are a subset of travelers with significant exposure to the risk of malaria. Despite current Department of Defense policy and provision of personal-protective measures and medicinal prophylaxis for service members operating in endemic regions, malaria continues to affect a significant proportion of at-risk service members. Military members should have access to recommended regimens for the treatment of malaria; however instances do occur where severe disease occurs in settings where resources are limited, diagnosis is difficult, and needed U.S. Food and Drug Administration (FDA) approved medications are scarce. Military healthcare providers should therefore be familiar with WHO-endorsed diagnostics and treatments available in malaria-endemic countries in situations where these services are needed while awaiting evacuation of a service member to a higher level military treatment facility. These guidelines provide recommendations for preparation and training prior to deployment to a malaria endemic area as well as evaluation, treatment, and management of a febrile service member at risk of malaria.

Each section begins with a question and is followed by numbered recommendations from the panel with strength and quality of supporting evidence ratings (Table 1). Treatment tables and algorithms are provided to guide use of these recommendations. Recommendations are supported by the evidence based review that follows the Executive Summary.

Appendix A: Diagnosis and Management of Malaria in U.S. Military Personnel in Resource Limited Setting: Clinical Practice Guidelines by the Armed Forces Infectious Disease Society

A. PREPARATION FOR DEPLOYMENT/TRAVEL

I. What Malaria-Specific Training Should Personnel Receive Before Deployment?

Recommendations

1. Antimalarial drug susceptibility patterns, recommended malaria prophylaxis and available antimalarial treatment regimens for the theater of operations should be included in pre-mission medical planning, using updated information from the National Center for Medical Intelligence (NCMI) (available at intelink.gov/ncmi/document.php?id=99003), the Centers for Disease Control and Prevention, and service specific policy. *(strong recommendation; low-quality evidence)*

2. Service members operating in endemic regions must have rapid access to effective antimalarials for the treatment of possible malaria. *(strong recommendation; high-quality evidence)*

3. Military medical providers and laboratory staff, deploying to malaria-endemic regions, should be properly trained to use and interpret RDTs. *(strong recommendation; low-quality evidence)*

4. Prior to deployment, military medical providers should establish a "reach-back" Infectious Disease consultant link that can be readily contacted throughout their deployment. *(strong recommendation; low-quality evidence)*

B. DIAGNOSTIC TESTING FOR MALARIA

II. When Should a Traveler or Service Member be Evaluated for Malaria?

Recommendations

5. Fever in U.S. military personnel, or other non-immune travelers, with current or recent travel to a malaria endemic region should prompt evaluation for malaria in addition to other possible non-specific febrile illnesses (including but not limited to dengue fever, early shigellosis, typhoid fever, rickettsiosis, leptospirosis or acute retroviral syndrome). *(strong recommendation; high-quality evidence)*

III. What Diagnostic Laboratory Tests Should be Used in Evaluation of an Individual with Suspected Malaria in a Deployed Setting?

Recommendations: *Malaria Blood Smears*

6. Microscopy is the gold standard diagnostic method for the detection of malaria. Thick and thin blood films should be prepared and read within a few hours, if possible. *(strong recommendation; high-quality evidence)*

7. High quality microscopic diagnosis of malaria is limited in both resource rich and resource poor settings. Blood films must be prepared using high quality materials and read by a microscopist skilled in reading malaria smears, and results should be available within 2 hours of blood specimen collection. *(strong recommendation; moderate-quality evidence)*

8. If microscopy is not available at the time of evaluation, slides should be prepared and saved and can be evaluated upon return to a more resource-rich setting to determine whether the individual had malaria and, if so, what species. *(strong recommendation, moderate-quality evidence)*

9. Blood smears should be obtained every 6-12 hours for a total of at least three sets, with the first and last obtained at least 24 hours apart. If all three are negative, the diagnosis of malaria is unlikely and evaluation for other possible etiologies should continue. *(strong recommendation; low-quality evidence)*

Recommendations: *Malaria Rapid Diagnostic Tests (mRDT)*

10. In remote settings, such as during military deployment, where expert microscopic diagnosis might not be available or is limited by technician experience, mRDTs may be used as a reasonable and useful alternative to malaria blood smears. *(strong recommendation; moderate-quality evidence)*

11. Most available mRDTs have reduced sensitivity at lower parasite densities. As with microscopy, a negative mRDT result should prompt repeat testing every 6-12 hours at the discretion of the provider if the clinical suspicion of malaria is high. *(strong recommendation; low-quality evidence)*

Recommendations: *Research Tests to Confirm an Unclear Diagnosis*

12. If possible, blood smears, dried blood spots (DBS) on filter paper, and whole blood should be obtained if the diagnosis of malaria or the species is unknown. These should be retained for species-specific diagnosis and antimalarial resistance testing at a later time. *(strong recommendation, moderate-quality evidence)*

C. TREATMENT OF MALARIA

IV. When Should Patients with Suspected Malaria be Treated in the Absence of a Positive Diagnostic Test for Malaria ("Presumptive Therapy")?

Recommendations

13. Providers evaluating an individual with fever and suspected malaria should attempt to contact an Infectious Diseases physician for assistance with diagnosis, treatment (especially if considering treatment with mefloquine), and determination of need for evacuation. If an ID consult is unavailable, this should be documented in the patient record and empiric therapy should be initiated. (*strong recommendation; weak-quality evidence*)

14. If the clinical suspicion of malaria is high, anti-malarial therapy should be started empirically ("presumptive therapy") while malaria and other possible etiologies are evaluated. *(strong recommendation; moderate-quality evidence)*

15. If reliable diagnostics are not readily available, presumptive therapy for malaria and other considered etiologies (e.g. doxycycline for leptospirosis and rickettsial diseases) should be initiated. Prompt, effective treatment and supportive care is critical to decrease mortality. *(strong recommendation; moderate-quality evidence)*

16. Severely ill patients should be treated with presumptive therapy for falciparum malaria while the evaluation is ongoing. *(strong recommendation; moderate-quality evidence)*

V. What Antimalarial Medication Should be Used to Treat Malaria?

Recommendations: *General Concepts*

17. Treatment should be guided by three factors: 1) the infecting *Plasmodium* species (either confirmed by microscopy or mRDT or presumed based on geographic location), 2) the clinical status of the patient (uncomplicated or complicated/severe) and 3) the malaria parasite drug susceptibility pattern of the geographic area where the infection was acquired. *(strong recommendation; moderate-quality evidence)*

18. If the infecting species cannot be confirmed or clinical suspicion is present in the absence of diagnostic capabilities, initial therapy should be directed against *P. falciparum*, using an appropriate antimalarial based on severity of illness and known local drug susceptibility pattern. *(strong recommendation; moderate-quality evidence)*

19. If a patient develops malaria while taking or after recently taking a specific antimalarial for prophylaxis, that same medication should NOT be used for treatment. *(weak recommendation, low-quality evidence)*

20. Medical officers should ensure that halofantrine is not used for military members with malaria who may require care in host country facilities prior to medical evacuation. *(strong recommendation; moderate-quality evidence).*

21. Substandard, degraded and counterfeit anti-malarial medications containing insufficient (or no) active ingredients or potentially toxic ingredients are highly prevalent throughout Southeast Asia and sub-Saharan Africa.

Recommendations: *Severe Malaria (any species)*

22. Intravenous artesunate (AS), followed by an oral antimalarial regimen, is the treatment of choice for severe malaria. *(strong recommendation; high-quality evidence)*

22a. Intravenous AS is not currently FDA-approved in the U.S. but is available through the U.S. CDC for cases of severe malaria under an investigational new drug (IND) protocol.

22b. Supplies of IV AS are positioned in Germany and South Korea for use in treating U.S. military members with severe malaria. U.S. embassies in many endemic areas also have a limited supply of IV AS that may be available in emergent cases.

22c. Clinicians must contact the CDC and their command pharmacy for approval, release and receipt of medication. Information and instructions for obtaining artesunate are contained in Section 5.

23. Intravenous quinidine gluconate is the only FDA-approved, licensed medication to treat severe and complicated malaria in the U.S. Because of the potential for severe cardiovascular side effects, it must be administered under careful clinical and electrocardiographic monitoring and is generally not available in the deployed setting. *(strong recommendation; high-quality evidence)*

24. Outside of the U.S., many non-FDA-approved drugs such as intravenous quinine (Q), intramuscular artemether, intravenous AS, and AS suppositories are used to treat severe malaria; all are efficacious and should be considered for treatment of severe malaria if AS or quinidine cannot be administered. However, providers should keep in mind that locally procured non-FDA-approved drugs can often be counterfeit or of substandard quality, and the efficacy can be highly variable between products. *(strong recommendation, high-quality evidence)*

25. Parenteral antimalarials should be given for a minimum of 24 hours and the parasite density, if known, is less than 1%. Once the patient can tolerate oral therapy and has received at least 24 hours of intravenous therapy for severe malaria, a full treatment course of an effective oral antimalarial should be administered. *(strong recommendation; moderate-quality evidence)*

Recommendations: *Uncomplicated P. falciparum (chloroquine-resistant or unknown)*

26. Atovaquone/proguanil (Malarone™) and artemether/lumefantrine (Coartem™) are both highly efficacious antimalarials for treating falciparum malaria. Treatment with atovaquone/proguanil (AP) is considered by many to be first line due to the ease of administration, likely increased compliance with once daily dosing, and superior safety profile. *(strong recommendation; moderate-quality evidence)*

27. Mefloquine (MQ), only for patients without a history of past or current neuropsychiatric disorders or cardiac conduction abnormalities, or oral Q in combination with either clindamycin or doxycycline are also accepted treatment regimens in the U.S.

Recommendations: *Uncomplicated P. falciparum (chloroquine-susceptible)*

28. Chloroquine (CQ) may be used to treat uncomplicated malaria acquired in regions with known CQ-susceptible *P. falciparum. (strong recommendation; moderate-quality evidence)*

Recommendations: *CQ-susceptible P. vivax and P. ovale*

29. CQ in combination with primaquine (PQ) is first line therapy for uncomplicated chloroquine-susceptible *P. vivax and P. ovale. (strong recommendation; high-quality evidence)*

30. Testing for glucose-6-phosphate dehydrogenase deficiency (G6PD) should be completed, or prior testing verified, before initiating PQ for radical cure. *(strong recommendation, moderate quality evidence)*

Recommendations: *CQ-resistant P. vivax (or uncertain area of exposure)*

31. MQ for treatment of individuals with no history of past or current neuropsychiatric disorders or cardiac conduction abnormalities, AP, artemether/lumefantrine (AL) and Q in combination with either clindamycin or doxycycline can be used to treat CQ-resistant *P. vivax*, followed by PQ for radical cure. *(strong recommendation; moderate-quality evidence)*

Recommendations: *P. malariae and P. knowlesi*

32. CQ is first line therapy for *P. malariae* and uncomplicated *P. knowlesi* infections. *(strong recommendation; low-quality evidence)*

Recommendations: *Mixed and Unknown Species Infections*

33. For malaria diagnosed in situations where the species cannot be determined in a timely manner or clinical suspicion is present in the absence of diagnostic capabilities, initial therapy should be directed against *P. falciparum*. Efforts should be made to identify the causative species so that PQ therapy can be provided as a radical cure, if needed. *(strong recommendation; moderate-quality evidence)*

34. If the species cannot be confirmed, radical cure with PQ should be provided based on the geographic likelihood of *P. vivax.*

D. LEVEL-OF-CARE MANAGEMENT DECISIONS

VI. When Does an Individual with Presumed or Confirmed Malaria Need to be Hospitalized?

Recommendations

35. Patients with suspected malaria should have the following rapid clinical screen to assess for warning signs of severe malaria:

a. Vital signs (blood pressure, pulse rate, temperature and respiratory rate)
   Does individual have any abnormalities suggesting hemodynamic instability or systemic inflammatory response syndrome that is unresponsive to fluid bolus or antipyretics?

b. Mental status
   Is individual confused or disoriented (if yes, concern for cerebral malaria)?

c. Respiratory status
   Is individual coughing, short of breath, or unable to speak in complete sentences or does individual have rales on physical examination (if yes to any, concern for pulmonary edema)?
   (strong recommendation, high-quality evidence)

36. Patients with uncomplicated malaria can generally be effectively treated with oral antimalarials, but must be monitored closely for progression of disease. *(strong recommendation; low-quality evidence)*

37. Need for hospitalization and in some cases, evacuation, should be dictated by the clinical manifestations (warning signs of severe malaria) and available resources in the field. *(strong recommendation; very low-quality evidence)*

38. Hospitalization of a non-immune patient with *P. falciparum* or *P. knowlesi* infection is often favored to allow close observation for tolerance of antimalarial therapy, monitoring of response to therapy with repeat blood smears, and advanced management in case of progression to severe disease. When hospitalization is not possible, patients should still be monitored closely for deterioration. *(strong recommendation; moderate-quality data)*

39. Oral antimalarials should be administered using directly observed therapy (DOT) in the non-hospital setting to ensure both compliance and appropriate response to therapy. *(strong recommendation; very low-quality data)*

VII. When Should an Individual with Severe Malaria be Admitted to an Intensive Care Unit or a Unit with Continuous Cardiorespiratory Monitoring?

Recommendations

40. Severe malaria is a medical emergency and military personnel with severe malaria should be promptly evacuated to a facility with an intensive care unit for supportive therapy as soon as possible, regardless of species identified. *(strong recommendation; low-quality evidence)*

VIII. How Should the Clinician Follow the Individual for Response to Therapy?

Recommendations

41. Individuals with uncomplicated malaria on adequate therapy may have an early increase in parasite density and symptoms after initiation of antimalarial therapy, but should demonstrate clinical improvement within 48 to 72 hours; asexual parasites should be undetectable in blood by day 4. Individuals whose condition continues to deteriorate or does not improve should undergo further investigation. *(strong recommendation; moderate-quality evidence)*

42. Failure to clear asexual parasitemia or recrudescence at any time during follow-up constitutes treatment failure, and clinicians should provide rescue therapy with an alternate agent. *(strong recommendation; moderate-quality evidence)*

43. In all cases of smear-diagnosed malaria, malaria smears should be obtained on days 1, 2, 3, and 4 or until negative for asexual forms. In areas with high concern for antimalarial resistance, such as the Thai/Myanmar border, Laos and Cambodia, smears should also be obtained on days 7 and 28 regardless of whether symptoms are present or not. *(strong recommendation; moderate-quality evidence)*

44. Malaria RDTs may remain positive for several weeks after starting anti-malarial therapy so should not be used to monitor response to therapy. *(strong recommendation; moderate quality evidence)*

IX. When Can an Individual Return to Duty After Being Diagnosed with Malaria?

Recommendations

45. Ability to return to duty should be at the discretion of the healthcare provider and should be based on the underlying health of the individual with malaria. *(strong recommendation, very low-quality evidence)*

Table 1. Strength of Recommendation and Quality of Evidence*

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable effects	Methodologic quality of supporting evidence (examples)	Implications
Strong recommendation			
High-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs[a] or exceptionally strong evidence from unbiased observational studies	Recommendations can apply to most patients in most circumstances; further research is unlikely to change our confidence in the estimate of effect.
Moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendations can apply to most patients in most circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for $\geq$ 1 critical outcome from observational studies, RCTs with serious flaws, or indirect evidence	Recommendations may change when higher quality evidence becomes available; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation			
High-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs[a] or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values; further research is unlikely to change our confidence in the estimate of effect and may change the estimate.
Moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches are likely to be better for some patients under some circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence for $\geq$ 1 critical outcome from observational studies, RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

[a]RCTs, randomized controlled trials

*Adapted from the Infectious Disease Society of America Guidelines Development Resources: GRADE Strength of Recommendations and Quality of the Evidence Table (available at http://www.idsociety.org/Guidelines_Other/)

Appendix B: Executive Order 13139

Federal Register
Vol. 64, No. 192
Tuesday, October 5, 1999

Presidential Documents

Title 3—

The President

Executive Order 13139 of September 30, 1999

Improving Health Protection of Military Personnel Participating in Particular Military Operations

By the authority vested in me as President by the Constitution and the laws of the United States of America, including section 1107 of title 10, United States Code, and in order to provide the best health protection to military personnel participating in particular military operations, it is hereby ordered as follows:

Section 1. *Policy.* Military personnel deployed in particular military operations could potentially be exposed to a range of chemical, biological, and radiological weapons as well as diseases endemic to an area of operations. It is the policy of the United States Government to provide our military personnel with safe and effective vaccines, antidotes, and treatments that will negate or minimize the effects of these health threats.

Sec. 2. *Administration of Investigational New Drugs to Members of the Armed Forces.*

(a) The Secretary of Defense (Secretary) shall collect intelligence on potential health threats that might be encountered in an area of operations. The Secretary shall work together with the Secretary of Health and Human Services to ensure appropriate countermeasures are developed. When the Secretary considers an investigational new drug or a drug unapproved for its intended use (investigational drug) to represent the most appropriate countermeasure, it shall be studied through scientifically based research and development protocols to determine whether it is safe and effective for its intended use.

(b) It is the expectation that the United States Government will administer products approved for their intended use by the Food and Drug Administration (FDA). However, in the event that the Secretary considers a product to represent the most appropriate countermeasure for diseases endemic to the area of operations or to protect against possible chemical, biological, or radiological weapons, but the product has not yet been approved by the FDA for its intended use, the product may, under certain circumstances and strict controls, be administered to provide potential protection for the health and well-being of deployed military personnel in order to ensure the success of the military operation. The provisions of 21 CFR Part 312 contain the FDA requirements for investigational new drugs.

Sec. 3. *Informed Consent Requirements and Waiver Provisions.*

(a) Before administering an investigational drug to members of the Armed Forces, the Department of Defense (DoD) must obtain informed consent from each individual unless the Secretary can justify to the President a need for a waiver of informed consent in accordance with 10 U.S.C. 1107(f). Waivers of informed consent will be granted only when absolutely necessary.

(b) In accordance with 10 U.S.C. 1107(f), the President may waive the informed consent requirement for the administration of an investigational drug to a member of the Armed Forces in connection with the member's participation in a particular military operation, upon a written determination by the President that obtaining consent:

(1) is not feasible;

(2) is contrary to the best interests of the member; or

(3) is not in the interests of national security.

Appendix C: DoD Instruction 6200.02 Application of Food and Drug Administration (FDA) Rules to the Department of Defense Force Health Protection Programs

Department of Defense
INSTRUCTION

NUMBER 6200.02
February 27, 2008

USD(P&R)

SUBJECT: Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs

References: (a) DoD Directive 6200.2, "Use of Investigational New Drugs for Force Health Protection," August 1, 2000 (hereby canceled)
(b) DoD Instruction 5025.01, "DoD Directives Program," October 28, 2007
(c) DoD Directive 5124.02, "Under Secretary of Defense for Personnel and Readiness," October 17, 2006
(d) Federal Food Drug and Cosmetic Act (FFDCA) (21 U.S.C. 301, et seq.)
(e) through (j), see Enclosure 1

1. PURPOSE

This Instruction:

1.1. Reissues Reference (a) as a DoD Instruction in accordance with the guidance in Reference (b) and the authority in Reference (c).

1.2. Updates policy and assigns responsibility for compliance with Reference (d); sections 1107 and 1107a of title 10, United States Code (U.S.C.) (Reference (e)); Executive Order 13139 (Reference (f)); and Parts 50, 56, 312, Subpart I of Part 314, Subpart G of Part 601 of title 21, Code of Federal Regulations (Reference (g)), for application of FDA rules to force health protection programs of the Department of Defense involving medical products required to be used under an Emergency Use Authorization (EUA) or an investigational new drug (IND) application.

1.3. Incorporates responsibilities of the Secretary of the Army as the Lead Component for the use of medical products under EUAs or IND applications.

Appendix D: NATO Medical Support Role Definitions, per NATO Logistics Handbook

1610. The term "Role" or "Echelon" is used to describe the stratification of the four tiers in which medical support is organised, on a progressive basis, to conduct treatment, evacuation, resupply, and functions essential to the maintenance of the health of the force. "Echelon" or "Role" is defined on the basis of capabilities and resources, and is not specific to particular medical unit types. The term "role" is used by land or air forces, while "echelon" is primarily a maritime term. While closely related, they are not exactly interchangeable. The treatment capability of each role/echelon is intrinsic at the higher level, e.g. a role 3 facility will have the ability to carry out role 2 functions. Each level of support has the responsibility to resupply and otherwise support the levels below them. There is no requirement that a patient must necessarily pass through each echelon of care in progression during treatment and evacuation.

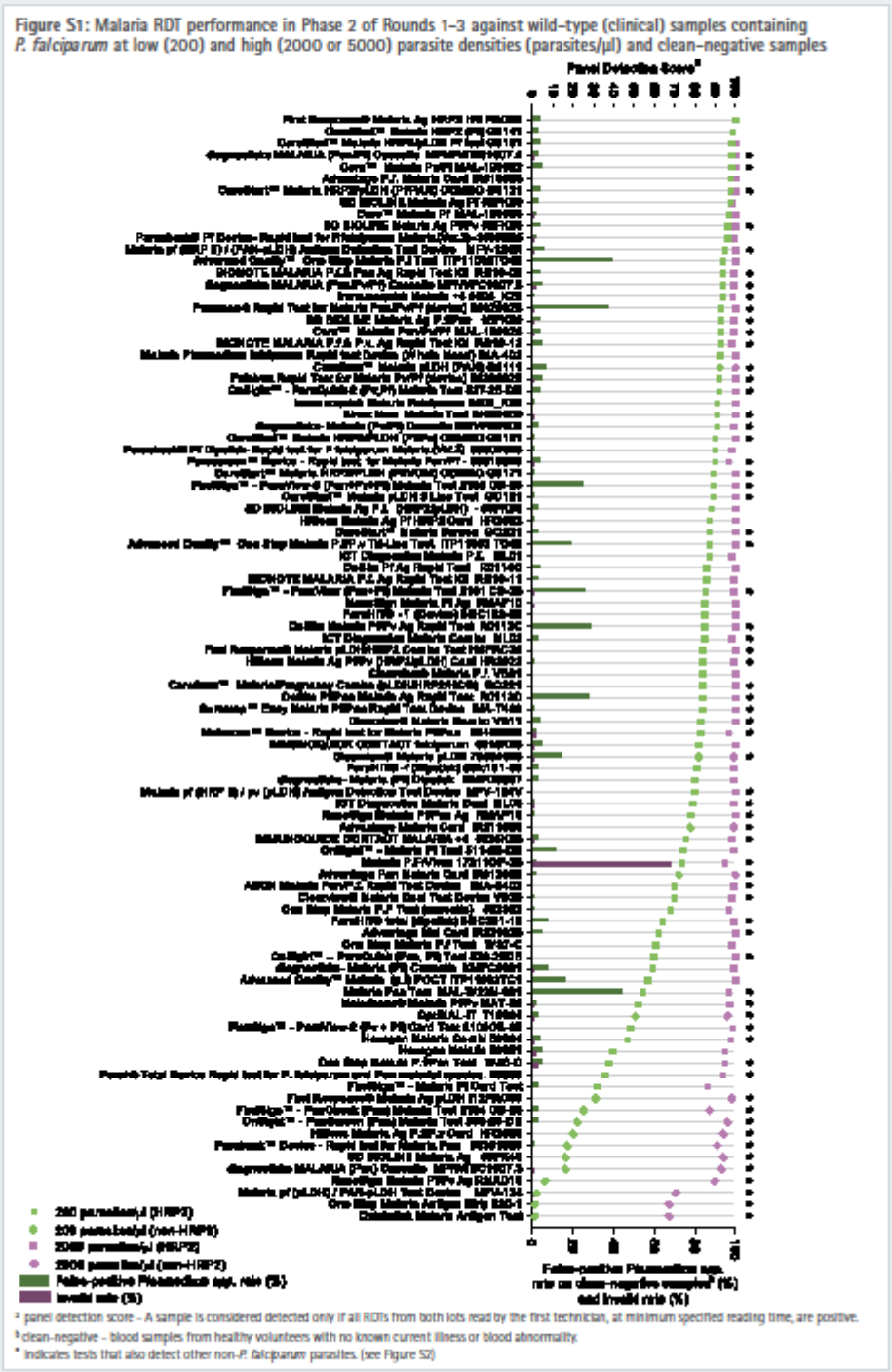
1611. Role/Echelon 1 medical support is that which is integral or allocated to a small unit, and will include the capabilities for providing first aid, immediate lifesaving measures, and triage. Additionally, it will contribute to the health and well-being of the unit through provision of guidance in the prevention of disease, non-battle injuries, and operational stress. Normally, routine sick call and the management of minor sick and injured personnel for immediate return to duty are a function of this level of care.

1612. Role 2 support is normally provided at larger unit level, usually of Brigade or larger size, though it may be provided farther forward, depending upon the operational requirements. In general, it will be prepared to provide evacuation from Role/Echelon 1 facilities, triage and resuscitation, treatment and holding of patients until they can be returned to duty or evacuated, and emergency dental treatment. Though normally this level will not include surgical capabilities, certain operations may require their augmentation with the capabilities to perform emergency surgery and essential post-operative management. In this case, they will be often referred to as Role 2+. In the maritime forces, Echelon 2 is equivalent to the land forces' Role 2+, as a surgical team is integral to this echelon. Maritime echelon 2 support is normally found on major war vessels and some larger logistics or support vessels, and at some Forward Logistics Sites (FLS).

1613. Role/Echelon 3 support is normally provided at Division level and above. It includes additional capabilities, including specialist diagnostic resources, specialist surgical and medical capabilities, preventive medicine, food inspection, dentistry, and operational stress management teams when not provided at level 2. The holding capacity of a level 3 facility will be sufficient to allow diagnosis, treatment, and holding of those patients who can receive total treatment and be returned to duty within the evacuation policy laid down by the Force Surgeon for the theatre. Classically, this support will be provided by field hospitals of various types. Maritime Echelon 3 is equivalent to land/air forces Role 3, though it will normally have increased specialty capabilities. Echelon 3 is normally found on some major amphibious ships, on hospital ships, at Fleet Hospitals, at some FLS, and at a few Advanced Logistics Support Sites (ALSS).

1614. Role/Echelon 4 medical support provides definitive care of patients for whom the treatment required is longer than the theatre evacuation policy or for whom the capabilities usually found at role/echelon 3 are inadequate. This would normally comprise specialist surgical and medical procedures, reconstruction, rehabilitation, and convalescence. This level of care is usually highly specialised, time consuming, and normally provided in the country of origin. Under unusual circumstances, this level of care may be established in a theatre of operations.

Appendix E: RDT Comparison Chart



Appendix F: DoD Instruction 6440.2 Clinical Laboratory Improvement Program (CLIP)

Department of Defense

INSTRUCTION

NUMBER 6440.2

April 20, 1994

ASD(HA)

SUBJECT: Clinical Laboratory Improvement Program (CLIP)

References: (a) Assistant Secretary of Defense (Health Affairs) Memorandum, "Policy Statement Implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88) within the Department of Defense (DoD)," October 8, 1993 (hereby canceled)

(b) Public Law 100-578, "Clinical Laboratory Improvement Amendments of 1988," October 31, 1988

(c) Memorandum of Agreement (MOA) between the Department of Defense and Department of Health and Human Services, "Implementation of the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88) within DoD," January 16, 1993

1. PURPOSE

This Instruction:

1.1. Supersedes reference (a).

1.2. Implements references (b) and (c) by establishing policy, assigning responsibilities, and prescribing procedures to implement and administer the CLIP within the Department of Defense.

1.3. Establishes the CLIP office at the Armed Forces Institute of Pathology (AFIP).

2. APPLICABILITY

This Instruction applies to the Office of the Secretary of Defense; the Military

Appendix G: Acronyms

AFHSC	Armed Forces Health Surveillance Center
AFIDS	Armed Forces Infectious Diseases Society
AFN	Armed Forces Network
AFPMB	Armed Forces Pest Management Board
AFRIMS	Armed Forces Research Institute for Medical Sciences
AMEDD	Army Medical Department
AOR	area of responsibility
ASD	Assistant Secretary of Defense
ASTMH	American Society of Tropical Medicine and Hygiene
ATP	atovaquone-proguanil
BUMED	Navy Bureau of Medicine and Surgery
CBMS	Chemical Biological Medical Systems
CDC	Centers for Disease Control and Prevention
CCMD	Combatant Commands
CLIA	Clinical Laboratory Improvement Amendments
CLIP	Clinical Laboratory Improvement Program
COTS	commercial, off-the-shelf
CPG	clinical practice guideline
DEET	Diethyl-*m*-toluamide
DHCC	Deployment Health Clinical Center
DHHS	Department of Health and Human Services
DMA	Defense Media Activity
DoD	Department of Defense
DoDI	Department of Defense Instruction
DOT	directly observed therapy
DTRA	Defense Threat Reduction Agency
FDA	Food and Drug Administration
FHP	force health protection
FHP&R	Force Health Protection & Readiness
GEIS	Global Emerging Infections Surveillance and Response System
GMO	general medical officer
IND	investigational new drug
IDSA	Infectious Disease Society of America
IPT	integrated planning team
JBAIDS	Joint Biological Agent Identification and Detection System
JHU/APL	Johns Hopkins University/Applied Physics Lab
MDA	Milestone Decision Authority
MDC	Malaria Diagnostics Center
MEF	Marine Expeditionary Force
MLT	Medical Laboratory Technician
MSMR	Medical Surveillance Monthly Report

Appendix G: Acronyms

NAMRU-2	Navy Medical Research Unit, Cambodia
NAMRU-3	Navy Medical Research Unit, Egypt
NAMRU-6	Navy Medical Research Unit, Lima
NAVAF	U.S. Naval Forces Africa
NCMI	National Center for Medical Intelligence
NECC	Naval Expeditionary Combat Command
NGDS	Next Generation Diagnostics System
NMCPHC	Navy & Marine Corps Public Health Center
NMRC	Naval Medical Research Center
OCONUS	outside the continental United States
O&M	Operations & Maintenance
OSD/HA	Office of the Secretary of Defense/Health Affairs
PART	presumptive anti-malarial relapse therapy
PCR	polymerase chain reaction
PPM	personal protective measures
R&D	research and development
RDT	rapid diagnostic test
SAGES	Suite for Automated Global Electronic bioSurveillance
TATRC	Telemedicine & Advanced Technology Research Center
TMA/OCMO	TRICARE Management Activity/Office of the Chief Medical Officer
TRL	Technology Readiness Level
USAFRICOM	U.S. African Command
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USAMRU-K	U.S. Army Medical Research Unit – Kenya
USAPHC	U.S. Army Public Health Command
USASOC	U.S. Army Special Operations Command
USUHS	Uniformed Services University of Health Sciences
WHO	World Health Organization
WRAIR	Walter Reed Army Institute for Research